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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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BOZICEVIC, FIELD & FRANCIS LLP
200 MIDDLEFIELD RD
SUITE 200
MENLO PARK, CA 94025

EXAMINER	
SULLIVAN, DANIEL M	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 03/20/2003

14

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/852,424	TUDAN ET AL.	
	Examiner	Art Unit	
	Daniel M Sullivan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 January 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) *5 and 10-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6-9,21 and 22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 May 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *8,9* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

This is a First Office Action on the Merits of the Application filed 9 May 2001 claiming benefit of U.S. Provisional Application 60/205,467 filed 19 May 2000 and Canadian Patent Application 2,305,787 filed 9 May 2000. Claims 1-22 are pending.

Election/Restrictions

Applicant's election of Group XXVI in Paper No. 13, filed 2 January 2003, is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 5 and 10-20 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 13.

Priority

Acknowledgment is made of applicant's claim for foreign priority based on an application filed in Canada on 9 May 2000. It is noted, however, that applicant has not filed a certified copy of the Canadian application as required by 35 U.S.C. 119(b).

Furthermore, Applicant has not complied with the requirements of 37 CFR 1.63(c), because, although the priority claim is made in the application data sheet, the Declaration indicates that priority to the foreign application is not claimed. To receive benefit of the foreign

application, a new oath or declaration is required in the body of which the present application should be identified by application number and filing date.

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

There is no support for a method of treating autoimmune disease in the Provisional application. Therefore, claim 22 will be afforded a priority date of 9 May 2001.

Claim Objections

Claim 9 objected to because of the following informalities: The claim is directed, in part, to non-elected subject matter. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4 and 6-8 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

In the instant case, the claims are directed to a method of using a compound having the activity of a CXCR4 antagonist. Thus, the claims encompass a method of using a genus of any and all compounds having the recited activity. The Guidelines for Written Description state "The claimed invention as a whole may not be adequately described if the claims require an essential or critical element which is not adequately described in the specification and which is not conventional in the art" (Federal Register, Vol. 66, No. 4, Column 3, page 71434). The CXCR4 antagonist of the instant invention is clearly a critical element of the claimed method and, thus, must be described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the full scope of CXCR4 antagonists.

The specification provides that the CXCR4 antagonists can be essentially any peptide or small molecule having the ability to bind to the CXCR4 receptor and prevent activation of the receptor by SDF-1 (e.g., paragraph bridging pages 27 and 28). Therefore the genus of CXCR4 antagonists encompasses a widely divergent set of compounds of unlimited structure. The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species, by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics (see MPEP 2163 (ii)). In the instant case, the disclosure provides a detailed structural description of several peptides derived from the N-terminal portion of SDF-1 (pages 15-26) and provides a single example of a small molecule having the activity of a CXCR4 antagonist (page 29). The disclosure also demonstrates inhibition of SDF-1 binding by 8 of the disclosed species of peptides, and a proliferative response elicited from primitive BFU-E and CFU-GM by 5 of the disclosed species. However, all of the peptide antagonists disclosed in the instant application comprise a portion of the N-terminus of SDF-1 wherein glycine is substituted for proline at position 2. The disclosure does not provide a single example of a peptide antagonist which does not comprise this structural feature, and therefore does not teach the relevant identifying characteristics of a peptide antagonist of CXCR4 which does not at least comprise the first 9 amino acids of SDF-1 wherein a glycine is substituted for proline at position 2 of the native peptide.

Beginning on page 15 and continued through page 29, the specification describes a variety of methods by which CXCR4 antagonists might be identified. However, an adequate written description of a molecule requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of

the molecule itself. It is not sufficient to define a molecule solely by its principal biological property, i.e. it has the activity of a CXCR4 antagonist as defined in the specification, because disclosure of no more than that, as in the instant case, is simply a wish to know the identity of any molecule with that biological property. Also, naming a type of material generically known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. Thus, claiming all molecules that achieve a result without defining what means will do is not in compliance with the description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)).

In view of these considerations, a skilled artisan would not have viewed the teachings of the specification as sufficient to show that the applicant was in possession of the claimed invention commensurate to its scope because it does not provide adequate written description for the broad class of CXCR4 antagonists. Therefore, only the described peptides comprising the first 9 amino acids of SDF-1 wherein a glycine is substituted for proline at position 2 of the native peptide or the small molecule set forth on page 29, meet the written description provision of 35 U.S.C. §112, first paragraph.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claims 1-4 and 6-9 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of promoting the rate of BFU-E or CFU-GM multiplication, does not reasonably provide enablement for a method of promoting proliferation

of any and all hematopoietic cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the nature of the invention; (b) the breadth of the claims; (c) the state of the prior art; (d) the amount of direction provided by the inventor; (e) the existence of working examples; (f) the relative skill of those in the art; (g) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue"; and (h) the level of predictability in the art (MPEP 2164.01 (a)).

Nature of the invention and breadth of the claims: The claims of the instant invention are directed to a method of promoting the rate of hematopoietic cell multiplication comprising administering an effective amount of a CXCR4 antagonist. The specification defines a hematopoietic cell as a "progenitor" cell possessing the ability to differentiate into a final cell-type directly or indirectly (paragraph bridging pages 5 and 6). The specification specifically identifies bone marrow stem or progenitor cells, lymphoid stem or progenitor cells, myeloid stem cells, CFU-GEMM cells, B stem cells, T stem cells, DC stem cells, pre-B cells, prothymocytes, BFU-E cells, BFU-MK cells, CFU-GM cells, CFU-bas cells, CFU-G cells, CFU-M/DC cells, CFU-Eo cells, CFU-E cells, myeloblasts, monoblasts, B-lymphoblasts, T-lymphoblasts, proerythroblasts, neutrophillic myelocytes, promonocytes, or other hematopoietic cells that differentiate to give rise to mature cells such as macrophages, myeloid related dendritic cells,

mast cells, plasma cells, erythrocytes, platelets, neutrophils, monocyhtes, eosinophils, basophils, B-cells T-cells or lymphoid related dendritic cells. The claims thus encompass a method of promoting the rate of proliferation of a widely divergent genus of cell types.

State and level of predictability in the art: The art of record at the time of filing does not provide a single example of a proliferative response to a CXCR4 antagonist. In contrast, Hodohara *et al.* (2000) *Blood* 95:769-775 teaches that SDF-1, acting through the CXCR4 receptor, stimulates megakaryopoiesis when administered in conjunction with thrombopoietin, and that antagonists of SDF-1 inhibit this response (see especially Table 2 and Table 6). Hodohara *et al.* conclude that SDF-1 acts directly on megakaryocytic progenitors to stimulate colony growth from bone marrow progenitor cells and, therefore, that the instant method would actually inhibit, rather than promote, hematopoietic cell multiplication. These teachings demonstrate that the relevant art at the time of filing was in an early stage of development and, given the teachings therein, the skilled artisan would not know how to obtain a proliferative response from the genus of hematopoietic cells set forth in the specification. Therefore, one of ordinary skill in the art must rely on the teachings of the instant disclosure to enable the claimed method.

Amount of direction provided by the inventor and existence of working examples: The instant disclosure teaches an increase in the number of cycling BFU-E and CFU-GM cells in response to CXCR4 antagonists (Example 2) and enhanced proliferation of these same cell types in an *in vivo* engraftment model (Example 3; Figure 2). However, the specification also teaches that the antagonists had no effect on the cycling status of long-term culture initiating cells (Figure 2). Therefore, although the it appears that the disclosure provides adequate guidance to

obtain a proliferative response from BFU-E and CFU-GM cells there are clearly examples of cells within the genus of hematopoietic cells that would not proliferate when treated according to the claimed method.

Relative skill of those in the art and quantity of experimentation needed to make or use the invention: Although the level of skill in the art is high, the teachings of the instant disclosure and prior art provide guidance that would enable the skilled artisan to practice the invention with only two species of the widely divergent genus encompassed by hematopoietic cells. Furthermore, the teachings provide that there are clearly examples of hematopoietic cells that would not proliferate in response to CXCR4 antagonists without additional manipulation. Because the specification and prior art is silent with regard to how to practice the invention with all hematopoietic cells, the skilled artisan would have to engage in empirical experimentation to discover how to promote the rate of multiplication of all hematopoietic cells. Given the large genus and the limited number of working examples, the degree of experimentation required would clearly be undue.

Claim 4 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Nature of the invention and breadth of the claims: Claim 4 is directed to a method of promoting the rate of hematopoietic cell multiplication further comprising introducing a heterologous gene into the hematopoietic cell for gene therapy. The specification does not set

forth any specific conditions to be treated according to the claimed method and thus encompasses a general method of treating any condition by gene therapy.

State of the prior art and level of predictability in the art: At the time of filing, gene therapy utilizing the direct administration of recombinant nucleic acids, regardless of the mode of delivery (e.g. adenovirus, retrovirus, liposome), was considered to be highly unpredictable. Verma et al. states that, "[t]he Achilles heel of gene therapy is gene delivery...", and that, "most of the approaches suffer from poor efficiency of delivery and transient expression of the gene" (Verma et al. (1997) *Nature* Volume 389, page 239, column 3, paragraph 2). Marshall concurs, stating that, "difficulties in getting genes transferred efficiently to target cells- and getting them expressed- remain a nagging problem for the entire field", and that, "many problems must be solved before gene therapy will be useful for more than the rare application" (Marshall (1995) *Science*, Vol. 269, page 1054, column 3, paragraph 2, and page 1055, column 1).

Orkin *et al.* further states in a report to the NIH that, " ... none of the available vector systems is entirely satisfactory, and many of the perceived advantages of vector systems have not been experimentally validated", and that," [w]hile the expectations and the promise of gene therapy are great, clinical efficacy has not been definitively demonstrated at this time in any gene therapy protocol" (Orkin *et al.* (1995) Report and recommendations of the panel to assess the NIH investment in research on gene therapy, page 1, paragraph 3, and page 8, paragraph 2).

Numerous factors complicate the gene therapy art which have not been shown to be overcome by routine experimentation. Eck *et al.* (1996) Goodman & Gilman's The Pharmacological Basis of Therapeutics, 9th Edition, Chapter 5, McGraw-Hill, NY, explains, "the delivery of exogenous DNA and its processing by target cells require the introduction of new

pharmakokinetic paradigms beyond those that describe the conventional medicines in use today". Eck *et al.* teaches that with *in vivo* gene transfer, one must account for the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced. These factors differ dramatically based on the vector used, the protein being produced, and the disease being treated (see Eck *et al.* bridging pages 81-82).

Also among the many factors that the art teaches affect efficient gene delivery and sustained gene expression are, immune responses and the identity of the promoter used to drive gene expression. Verma et al. teaches that weak promoters produce only low levels of protein, and that only by using appropriate enhancer-promoter combinations can sustained levels of therapeutically effective protein expression be achieved (Verma et al., *supra*, page 240, column 2). Verma et al. further warns that, "...the search for such combinations is a case of trial and error for a given type of cell" (Verma et al., *supra*, page 240, bridging sentence of columns 2-3). The state of the art is such that no correlation exists between successful expression of a gene and a therapeutic result (Ross et al. Human gene Therapy, vol. 7, pages 1781-1790, September 1996, see page 1789, column 1, first paragraph). Thus, the art at the time of filing clearly establishes that expectation for achieving a desired therapeutic effect *in vivo* by expressing a therapeutic

gene using any of the expression constructs known in the art at the time of filing was extremely low.

In an article published well after the effective filing date of the instant application, Rubanyi (2001) *Mol. Aspects Med.* 22:113-142 teaches that the problems described above remained unsolved at the time the instant application was filed. Rubany states, "[a]lthough the theoretical advantages of [human gene therapy] are undisputable, so far [human gene therapy] has not delivered the promised results: convincing clinical efficacy could not be demonstrated yet in most of the trials conducted so far..." (page 113, paragraph 1). Among the technical hurdles that Rubany teaches remain to be overcome are problems with gene delivery vectors and improvement in gene expression control systems (see especially "**3. Technical hurdles to be overcome in the future"**, beginning on page 116 and continued through page 125).

Beyond the technical barriers common to all gene therapy approaches, each disease to be treated using gene therapy presents a unique set of challenges that must be addressed individually. The claims of the instant application are not limited to treatment of any particular condition and thus encompass methods of treating any and all conditions that might be amenable to gene therapy. However, Rubanyi teaches, "each disease indication has its specific technical hurdles to overcome before gene therapy can become successful in the clinic" (page 131, third full paragraph). Rubanyi states, "the most promising areas for gene therapy today are hemophilias, for monogenic diseases, and cardiovascular disease (more specifically, therapeutic angiogenesis for myocardial ischemia and peripheral vascular disease...) among multigenic diseases" (page 113, fourth paragraph). As of the filing date of the instant application, however,

even these most promising areas presented barriers to successful gene therapy that could not be traversed by routine experimentation.

With regard to hemophilia, Schwaab *et al.* (2001) *Semin. Thromb. Hemost.* 27:417-424 teach that immune response against gene therapeutically administered Factor VIII and Factor IX compromised the success of therapy in many animal studies and that, "the situation is still more complicated by the fact that hemophilia B-affected dogs that have been intravenously treated with canine Factor IX protein without immune response against canine Factor IX develop antibodies when treated by gene therapy" (page 421, first paragraph in column II). Schwaab *et al.* also affirms that gene delivery remains a substantial problem in the development of gene therapy for hemophilia (see especially the second paragraph in column 2 on page 421). In subsequent discussion of ongoing clinical trials of gene therapy for hemophilia A and B, Schwaab *et al.* teach that, as of 2001, the effectiveness of gene therapy as a treatment for hemophilia had not been established (see beginning the final paragraph on page 421 and continued through the first paragraph of the second column on page 422). These teachings demonstrate that, as of the time of filing, successful treatment of hemophilia using gene therapy was unpredictable regardless of the delivery method employed.

With regard to gene therapy of ischemia, Rissanen *et al.* (2001) *Eur. J. Clin. Invest.* 31:651-666, teaches that although applications of therapeutic angiogenesis for ischemic disorders has established the proof of principle that exogenous growth factors can augment circulatory defects in animals and man, many important questions remain to be addressed. "Firstly, mechanisms of collateral growth by exogenous growth factors are still unclear...[a]dditional factors...may be required for collateral formation and maintenance of functional blood vessels.

Secondly, the persistence of new vessels is unknown after transient gene expression. Thirdly, improvement is needed in gene transfer efficiency..." (paragraph bridging pages 659 and 660). Emanueli *et al.* (2001) 133 :951-958 further teach that, "[d]elivery of angiogenic inducers...in ischaemic tissues allows rescue of blood perfusion. However, angiographic studies clearly show that the newly formed vasculature is abnormal and not well organized as in normal tissues...resembling the characteristics of leaky haemangiomas..." (page 955, the paragraph bridging columns 1 and 2). These teachings show that, even in an area of gene therapy considered promising, significant obstacles to successful therapy remained well after the effective filing date of the instant application.

Thus, the art at the time of filing clearly establishes that expectation for achieving a desired therapeutic effect *in vivo* by expressing a therapeutic gene using any of the expression constructs known in the art at the time of filing was extremely low.

Amount of direction provided by the inventor existence of working examples: The teachings of the specification provide only that CXCR4 antagonists promote the rate of BFU-E and CFU-GM cell multiplication. The disclosure does not demonstrate that the method in any way addresses the myriad of obstacles remaining to be traversed before the skilled artisan could use the claimed method for gene therapy.

Relative skill of those in the art and quantity of experimentation needed to make or use the invention: Although the level of skill in the art is high, given the high degree of unpredictability in the gene therapy art, the skilled artisan would not be able to use the methods of the instant claim 4 without first engaging in undue experimentation. While it is relatively routine in the gene transfer art to achieve expression at non-therapeutic levels (i.e. levels

providing no patentably useful phenotypic effect), the skilled artisan would have to engage in trial and error experimentation to achieve expression of a particular molecule at levels sufficient for therapeutic effect. Given the many factors affecting gene transfer and expression *in vivo* and the absence of existing working examples the level of experimentation required is clearly beyond what is considered routine in the art. Therefore, the teachings of the specification and prior art would not enable the ordinary skilled artisan to use the invention without undue experimentation.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 21 and 22 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are indefinite in that they do not set forth a terminal process step that clearly relates back to the preamble of the claim. That is, the body of the claims set forth administering the CXCR4 antagonist to promote hematopoietic cell multiplication and not treatment of cancer or autoimmune disease

In addition, claim 22 appears to be asserting that there is a nexus between the administration of an effective amount of a CXCR4 antagonist to promote the rate of hematopoietic cell multiplication and an effective treatment of autoimmune disease. However, the disclosure provides no basis for therapeutic efficacy based on hematopoietic cell multiplication. It is therefore unclear why the claim should be limited to administering an

effective amount to promote the rate of hematopoietic cell multiplication and not to an effective amount to treat an autoimmune disease.

Claim Rejections - 35 USC § 103

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 22 is rejected under 35 U.S.C. 103(a) as being unpatentable over Gonzalo (2000) *J. Immunol.* 165:499-508 in view of either one of Buckley *et al.* (2000) *J. Immunol.* 165:3423-3429 or Nanki *et al.* (2000) *J. Immunol.* 165:6590-6598 and in further view of Loetscher *et al.* (1998) *J. Biol. Chem.* 273:22279-22283.

The claim is directed to a method of treating an autoimmune disease in a patient comprising administering an effective amount of a CXCR4 antagonist. The teachings of Nanki *et al.* and Buckley *et al.* demonstrate upregulation of CXCR4 in synovial tissue $CD4^+$ T cells in rheumatoid arthritis. Buckley teaches, "the persistent and inappropriate induction of CXCR4 by stromal-derived factors such as TGF-β leads to the active SDF-1-driven retention of CD4 T cells in a perivascular distribution within the rheumatiod joint (paragraph bridging pages 3428 and 3429). Nanki *et al.* teaches that the findings presented therein suggest, "CXCR4-SDF-1 interactions might play a central role in memory T cell migration into the inflamed RA synovium and for persisting inflammation at this site mediate by $CD4^+$ T cells (final paragraph on page 6597). Gonzalo *et al.* teaches that neutralizing CXCR4 antibodies reduced mononuclear cell and eosinophil accumulation (see especially Figures 3 and 4 and Table 1) and improves airway function in a mouse model of allergic airway disease. Thus, at the time the instant application was filed, it was known in the art that CXCR4 is expressed in $CD4^+$ T cells present in the rheumatoid joint, as is SDF-1, and that SDF-1-CXCR4 is likely involved in retention of $CD4^+$ T cells in rheumatoid arthritis. Further, it was known that CXCR4 neutralizing antibodies effectively suppress inflammatory disease. The claimed method would therefore have been obvious to one of ordinary skill in the art at the time the instant invention was made. The teachings of Gonzalo *et al.* provide a method of suppressing inflammatory disease by administering a CXCR4 antagonist. The teachings of Buckley *et al.* and Nanki *et al.*, which indicate a role for SDF-1-CXCR4 in maintaining inflammation in rheumatoid arthritis, provides motivation to apply the method of Gonzalo *et al.* to the treatment of the autoimmune disease rheumatoid arthritis. Absent evidence to the contrary, one would have a reasonable expectation

of success in combining these teachings in view of the teachings from Gonzalo *et al.* indicating that CXCR4 neutralizing antibodies are effective inhibitors of inflammation, and the teachings from Buckley *et al.* and Nanki *et al.* indicating a role for SDF-1-CXCR4 in the rheumatoid arthritis.

Although the claim is not specifically limited to a method of treatment comprising administering a peptide antagonist derived from the N-terminus of SDF-1, the limitation would be obvious to the ordinary skilled artisan at the time of filing in view of the teachings of Loetscher *et al.* Loetscher *et al.* teaches an SDF-1, 1-9 analogue antagonist of CXCR4 (see especially the first full paragraph in the second column on page 22281, and figures cited therein). Loetscher *et al.* further teaches, "stable low molecular weight nonapeptide ligands are preferred for therapeutic applications" (second full paragraph on page 22283). Thus Loetscher *et al.* provides both an SDF-1, 1-9 analogue antagonist of CXCR4 and motivation to substitute this antagonist for the neutralizing antibodies of Gonzalo *et al.* A method of treating an autoimmune disease comprising administering an SDF-1, 1-9 analogue antagonist of CXCR4 would therefore have been obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 703-305-4448. The examiner can normally be reached on Monday through Friday 8-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 703-305-1998. The fax phone numbers for the

organization where this application or proceeding is assigned are 703-746-9105 for regular communications and 703-746-9105 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

dms
March 19, 2003

Anne-Marie Falk

ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER